UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

Date: October 30, 2014

SUBJECT: **Pirimiphos-Methyl:** Summary of the Hazard and Science Policy Council (HASPOC): Recommendations on the Need for a Subchronic Inhalation Toxicity Study.

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10/30/14

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MEETING ATTENDEES

HASPOC Members: Anna Lowit, Jeff Dawson, Elissa Reaves, Jonathan Chen, Jeff Dawson, Jess Rowland, John Kough, Michael Metzger, Kristin Rury, Jonathan Leshin, Monique Perron

Presenters: Karlyn Middleton, Zaida Figueroa

I. PURPOSE OF MEETING:

Risk Assessment Branch II (RAB II) is currently preparing a preliminary human health risk assessment for pirimiphos-methyl. Pirimiphos-methyl is a member of the organophosphate (OP) class of pesticides. Like other OPs, the initiating event in the adverse outcome pathway (AOP)/mode of action (MOA) for pirimiphos-methyl involves inhibition of the enzyme acetylcholinesterase (AChE) via phosphorylation of the serine residue at the active site of the enzyme. This inhibition leads to accumulation of acetylcholine and ultimately to neurotoxicity in the central and/or peripheral nervous system. For pirimiphos-methyl, red blood cell (RBC) AChE inhibition is the most sensitive endpoint in the toxicology database in multiple species, durations, lifestages, and routes. Therefore, the risk assessments are based on RBC AChE inhibition (Table 1a and 1b, Attachment A).

The toxicology database for pirimiphos-methyl is adequate for risk assessment. Immunotoxicity and inhalation studies are not available for pirimiphos-methyl. The Hazard and Science Policy Council (HASPOC) previously waived the immunotoxicity requirement for organophosphates (TXR# 0056738), including pirimiphos-methyl. Cholinesterase inhibition is the endpoint of concern for pirimiphos-methyl and comparative acute and repeat dose cholinesterase studies are available for pirimiphos-methyl; however, the studies do not include a gestational component which is needed for comparative AChE evaluation of pregnant dams and fetuses. The data is required for OPs (U.S. EPA 1999, 2002). The HASPOC met on June 5, 2014 to discuss the need for the inhalation study required in accordance with the 2007 Part 158 Toxicology Data Requirements.

II. SUMMARY OF USE PROFILE

Pirimiphos-methyl is registered for post-harvest insect control on stored corn (field, seed, and pop) and grain sorghum (including bulk or bagged seed) going into storage or shipping containers, and ready-to use (RTU) ear-tag treatment of livestock. There are also special local need labels for uses on iris in Washington State and gladiola bulbs in Michigan State. The major use of pirimiphos-methyl is for the post-harvest grain and seeds going into storage or export containers in the South and warmer climates. It is applied at the point of transfer (between August and September) and the treated seed grain is usually stored for 8-9 months before planting (May). Currently, there are no registered uses of pirimiphos-methyl that could result in residential exposure, and there is no concern for spray drift based on the use pattern.

III. STUDY WAIVER REQUESTS

a. Inhalation Toxicity Study

Previously, the Office of Pesticide Programs (OPP) used a set of criteria to determine whether or not an inhalation study could be waived. These criteria considered the scientific information available for the chemical, including its: (1) degree of irritation and corrosivity; 2) volatility; 3) aerosol particle size; and 4) Acute Toxicity Category and extrapolated MOEs (e.g., MOEs 10 times higher than the target). In 2009, OPP developed an issue paper on risk assessment approaches for semi-volatile pesticides. As part of that issue paper, an analytical comparison was conducted of

oral and inhalation experimental toxicology studies. In general, this analysis showed that the degree to which oral PoDs were protective of potential inhalation toxicity varied. In many cases the oral PoD was protective, but in some cases the inhalation PoDs were significantly more sensitive. Currently, OPP uses a weight of the evidence (WOE) approach that builds upon OPP's experience using the criteria listed above and conclusions from the 2009 SAP. As approaches for route-to-route extrapolation continue to evolve and improve, OPP may incorporate additional considerations into the WOE analysis.

Inhalation exposure can be to vapors, droplets, and/or particles/dusts. The form of inhalation exposure is determined by a number of factors including physical-chemical properties, use pattern, and exposure scenarios. OPP's interim WOE approach considers:

1. **Physical Chemical Properties:** Vapor pressure and Henry's law constant are key considerations with respect to the volatilization after sprays have settled. Pirimiphos-methyl (305.3 g/Mol) has a high vapor pressure of 1.1×10^{-4} mm Hg at 30° C and a Henry's Law constant of 6.0×10^{-2} Pa m^3 mol^{-1}.

2. **Use pattern & exposure scenarios:** Any application scenario that leads to inhalation exposure to droplets needs to be considered in the WOE analysis for an inhalation toxicology study waiver request. Pirimiphos-methyl is registered for post-harvest use on stored corn (field, seed, and pop) and grain sorghum (including bulk or bagged seed), and RTU ear-tag treatment of livestock. There are also special local need labels for uses on iris in Washington and gladiola bulbs in Michigan.
   The major use of pirimiphos-methyl is for the post-harvest control of insects in grain and seeds going into storage or shipping containers. It can also be used top dressing stored grain once in storage areas. Treatment of seedcorn is only allowed off-farm (e.g., in a facility where seed is bagged). Currently, there are no registered uses of pirimiphos-methyl that could result in residential exposure and there is no concern for spray drift.

   Occupational inhalation exposures are expected for workers treating stored seeds and grains (primary and secondary handlers; e.g., loader/applicator, sewer, bagger, multiple activities worker and planters), and for mixer/loader and applicators during top-dressing (surface spray) seed treatment. Only one registered label allows for top dressing applications. Also, handler inhalation exposures are expected for mixer/loader during greenhouse (indoor) stationary fogger applications. Negligible inhalation exposures are expected for workers applying RTU ear-tag to cattle.

   Margins of Exposure (MOEs): MOE estimates for inhalation scenarios were calculated using an oral toxicity study and should be considered in the WOE analysis for an inhalation toxicology study waiver request. In the past, OPP has used MOEs of approximately 10 times higher than the level of concern as a benchmark for granting waiver requests. The 2009 analysis suggests this approach is appropriate for most pesticides but not all. Using this interim WOE approach, MOEs from 10-100 times greater than the level of concern will be considered in combination with other factors discussed here. All handler inhalation exposure MOEs were based on an oral repeat rat cholinesterase assay (CCA) study with a $BMDL_{10}$ of 0.73 mg/kg/day (BMD_{10}=1.01 mg/kg/day), based on inhibition of RBC AChE

in PND 21 pups. The pup value was selected for risk assessment since values were slightly lower than adults. However, no sensitivity was seen regarding adult and pup RBC and brain cholinesterase inhibition in the study after repeat exposure. The LOC for the HASPOC WOE is 3000X for worker inhalation assessment for pirimiphos methyl derived from the typical 100X uncertainty factors (10X interspecies, 10X intraspecies) with an additional 30X database uncertainty factor for the lack of gestational ChE data, and the lack of inhalation study. Handler inhalation MOEs ranged from 820 to 1,200,000 (see Tables 2a and 2b, Attachment A). The lowest MOE is for mixer/loaders/applicators conducting a top-dressing (surface spray) seed treatment application using a manually-pressurized hand wand at baseline PPE (i.e., no respirator). When the level of mitigation or PPE is increased to a PF5 respirator, the inhalation risk estimate results in a MOE of 4,100. Only one registered label allows for top dressing applications. The label doesn't require handlers to wear a respirator.

3. TOXICITY PROFILE:

Pirimiphos-methyl inhibits cholinesterase activity in various species including rats, mice, rabbits, and dogs. Based on high quality dose response data, across multiple lifestages, durations, and routes of exposure, pirimiphos-methyl causes dose-related inhibition in red blood cell (RBC) and brain acetylcholinesterase (AChE) activity. The available guideline oral and dermal toxicology studies and comparative cholinesterase assay (CCA) study for pirimiphos-methyl demonstrate that RBC AChE inhibition occurs at doses lower (ie., more sensitive) than brain AChE inhibition. Generally, there were no major sex differences between male and female values, with the exception of brain AChE inhibition which was slightly higher in adult males compared to females.

Pups were more sensitive than adults to RBC and brain AChE inhibition after acute exposure. However, adult and pup RBC and brain cholinesterase inhibition values were generally comparable after repeated exposure, with the exception of a slightly higher BMD value for male adult brain cholinesterase inhibition. None of the guideline developmental and reproduction toxicity studies for pirimiphos-methyl demonstrated quantitative and/or qualitative susceptibility.

Limited gestational AChE data are available for rabbits. However, no gestational AChE data are available in rats or in fetal animals (rat or rabbit). A DNT study has been waived for pirimiphos-methyl.

Clinical signs of neurotoxicity were observed in the toxicology database at doses higher than AChE inhibition.

Pirimiphos-methyl is classified as "not likely to be carcinogenic to humans" and there is no concern for mutagenicity.

In acute lethality studies (LD_{50}), pirimiphos-methyl has low toxicity (Toxicity Category III) via oral, dermal, and inhalation routes of exposure. It is an eye irritant (Toxicity Category II) and moderate dermal irritant (Toxicity Category III); it is not a dermal sensitizer. In the

acute LD_{50} inhalation study, Albino rats were exposed to 5.04 mg/L (876 mg/kg/day) of the technical ingredient by nose only administration for 4 hours. Clinical signs and RBC inhibition were seen in the study; however, no deaths were reported. Pirimiphos is classified as a category IV for acute inhalation exposure.

Although an inhalation toxicity study is not available for pirimiphos-methyl, inhalation studies are available for a number of organophosphates. The inhalation studies are commonly used for inhalation risk assessment and the inhalation PODs are based on AChE inhibition.

V. HASPOC CONCLUSIONS

Based on a WOE approach and considering all of the available pirimiphos-methyl hazard and exposure information, the HASPOC concludes that a subchronic inhalation toxicity study be required for pirimiphos-methyl since:1) there is potential for repeated inhalation exposure; 2) there is potential for volatilization based on the high vapor pressure; 3) using the current oral POD, the MOE for occupational handler,-top dressing seed treatment application is below the LOC of 3,000; 4) top dressing seed treatment application is a common practice based on one registered label and comments submitted by the registrant in response to the pirimiphos-methyl registration review preliminary work plan (EPA-HQ-OPP-2009-0056).

For all inhalation risk assessments, a 10X UF_{DB} will be retained until data or information become available to fill the data need. Until the data are fulfilled and in the absence of the required data, the agency has established a maximum UF composite of 3000X for worker inhalation assessment for pirimiphos methyl until data or information are provided to fulfill the data needs.

The composite UF for is derived from the typical 100X uncertainty factors (10X interspecies, 10X intraspecies) with an additional 30X database uncertainty factor for the lack of gestational ChE data, and the absence of the inhalation study. The inhalation assessment is currently based on an oral repeat rat cholinesterase assay (CCA) in pups. Although the pup value was selected for risk assessment, no sensitivity was seen in the study regarding adult and pup RBC and brain cholinesterase inhibition after repeat exposure.

VI. REFERENCES

US EPA. Data Call-In notice, Attachment F. September 10, 1999.

US EPA. 2002. Guidance on Cholinesterase Measures in DNT and Related Studies. Health Effects Division, Office of Pesticide Programs. October 22, 2002.